REMARKS

Amendment of the claim

Claim 7 is amended to restore the inadvertently omitted limitation requiring that the labeled murine antibody be an anti-CD20 antibody. The amendment is supported by the disclosure as filed, including the original claims. No new matter is introduced by this amendment.

Objection to the previous amendment

Claim 7 was objected to for an improper amendment format. In particular, the words "anti-CD20," which had been present in the previous version of the claim, were not repeated or indicated as deleted in the amendment filed on 9 February 2005.

Because the claim filed on 9 February 2005 was entered as presented, the amendment set forth above shows changes relative to that claim. Applicant believes that the present amendment obviates the basis for the objection.

Rejection under 35 U.S.C. § 112, first paragraph

Claim 7 was rejected as not supported by an enabling disclosure commensurate in scope with the amended claim. The examiner stated that the scope of the claim prior to amendment (*i.e.*, limited to methods involving the administration of anti-CD20 antibodies) was supported in the manner required by § 112. Thus, applicant understands that the entire basis for the rejection is the inadvertent omission of the "anti-CD20" limitation. Accordingly, applicant believes that the amendment set forth above fully responds to the stated rejection and requests that the examiner withdraw the same.

Rejection under 35 U.S.C. § 103

The examiner maintains the rejection of claim 7 under § 103 based on Maloney *et al.* (*Blood*, 1995) in view of one of Press *et al.* (*Lancet*, 1995), Kaminsky *et al.* (*J. Clin. Oncol.*, 1996) ("1996"), or Kaminsky (U.S. Patent No. 6,287,537) ("'537"); further in view of Wahl *et al.* (ASCO abstract, 1998). Applicant respectfully traverses.

The rejection appears to depend on the examiner's determination that Maloney identifies patients who are "refractory" to rituximab therapy. In particular, the examiner finds that the patients who are reported not to respond to rituximab must be refractory. Applicant does not agree with this finding.

The concepts of "nonresponsive" and "refractory" have distinct meanings for therapeutic oncologists. "Refractory" requires more than simply the absence of a response. For example, a given patient might not respond (or might not respond fully) to a standard dose of a particular therapeutic agent, but would respond to a higher dose of the same agent. Such a patient would be described as a nonresponder to the standard dose, but would not qualify as refractory. A refractory patient is one who is not expected to respond to the therapy at all.

Typically, patients (or more precisely, the tumors they carry) are described as refractory after they first exhibit an effective response to a drug, and later do not show a comparable response to the same drug. Such patients would be both relapsed and refractory. In the case of therapeutic anti-CD20 antibodies, it is reasonable to expect that patients having tumors that are not CD20-positive would be refractory to those antibodies, at least so long as the tumor cells continued not to express CD20.

It is possible that some of the patients reported in the Maloney trial were genuinely refractory to rituximab therapy, but the information provided in the reference does not reasonably allow one to reach that conclusion. All that one can say is that certain patients did not respond to the trial protocol.

Apart from the fact that Maloney does not disclose that any of the treated patients are refractory to rituximab, applicant does not agree that it would have been obvious to treat any of the nonresponsive patients from the Maloney study with a radiolabeled antibody. The examiner relies on the disclosure in Kaminsky that certain subjects exhibited a response to anti-B1 antibody therapy only after a radiolabeled anti-B1 antibody was administered. It is improper to generalize this disclosure to a teaching that any subject that fails to respond to a dose of unlabeled anti-CD20 antibody may be effectively treated by administering [^{131}I]-anti-B1.

To fully combine the teachings of Maloney and the cited secondary references, it would be necessary to administer a "saturating" dose of unlabeled anti-B1 antibody before administering the radiolabeled antibody. This is so because Kaminsky teaches that the

"saturation" is responsible for the observation that certain subjects only respond to a follow-up dose of [^{131}I]-anti-B1 and, indeed, is necessary to provide the full therapeutic benefit of the radiolabeled anti-CD20 therapy.

The present claim is limited to the treatment of rituximab-refractory patients. It would not have been obvious to administer a saturating dose of an unlabeled anti-CD20 antibody to any patient already known to be refractory to therapy with an unlabeled anti-CD20 antibody, rituximab. One would expect no benefit from the therapeutic regimen, and a clinician would not administer a large amount of a protein drug that would be expected to be without effect. Accordingly, the references provide no motivation to combine their teachings in a manner that would lead to the practice of the claimed invention.

For these reasons and for the reasons set forth in the reply filed on 9 February 2005, applicant maintains that the examiner has not set forth a *prima facie* case of obviousness. Applicant requests that the examiner withdraw the outstanding rejection.

Conclusion

Applicant believes that this reply fully responds to the outstanding Office action and requests reconsideration and allowance of the pending claim.

Applicant requests a personal interview with the examiner to discuss any remaining issues concerning the outstanding rejection under 35 U.S.C. § 103.

The examiner is invited to contact the undersigned with any questions regarding the application.

Respectfully submitted,

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